Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
C1-A0304P		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/JP2004/008585	11.06.2004	11.06.2003

International Patent Classification (IPC) or national classification and IPC

Applicant

CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

_____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/008585

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/008585

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted the claims nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

The matter common to independent claims 1, 2 and 11 to 13 (invention group A) relates to that, in producing an antibody comprising a first pair and a second pair, the contact of the first light chain not bonded to the first heavy chain with the second heavy chain not bonded to the second light chain and the contact of the first heavy chain not bonded to the first light chain with the second light chain not bonded to the second heavy chain are inhibited by, for example, expressing the first pair and the second pair at different timings. The matter common to independent claims 3 and 4 (invention group B) relates to a process for producing an antibody comprising the step of forming a first pair, the step of forming a second pair and the step of forming the antibody with the use of the first and second pairs. The matter common to independent claims 9 and 18 (invention group C) relates to a vector wherein the expression of the

(continued in supplemental box)

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. _____

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/008585

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 2, 9, 11-13, 18	YES
	Claims	3-8, 10, 14-17, 19, 20	NO
Inventive step (IS)	Claims		YES
	Claims	1-20	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: Carter, P. et al., "Bispecific human IgG by design", J. Immunol. Methods, 2001, Vol. 248, pages 7 to 15

Document 2: Ridgway J.B. et al., "'Knobs-into-holes' engineering of antibody CH3 domains for heavy chain heterodimerization", Protein Eng., 1996, Vol. 9, pages 617 to 621

Document 3: Peipp M. et al., "Bispecific antibodies targeting cancer cells", Biochem. Soc. Trans., 2002, Vol. 30, pages 507 to 511

Document 4: Shalaby M.R. et al., "Development of humanized bispecific antibodies reactive with cytotoxic lymphocytes and tumor cells overexpressing the HER2 protooncogene", J. Exp. Med., 1992, Vol. 175, pages 217 to 225

Document 5: Skerra A. et al., "Use of the tetracycline promoter for the tightly regulated production of a murine antibody fragment in Escherichia coli", Gene, 1994, Vol. 151, pages 131 to 135

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

Claims 3 to 8

The invention set forth in claims 3 to 8 lacks novelty in the light of documents 1 and 2 cited in the international search report.

Documents 1 and 2 are understood to disclose a process for producing bispecific antibody into which knobs-into-hole has been introduced, containing a step of preparing a first pair disclosed in this application, a step of preparing a second pair disclosed in this application, and a step of preparing antibodies using said first pair and second pair.

Here, the process for producing an antibody set forth in claim 3 of this application, in the light of this disclosure, is a production process containing steps (a), (b) and (c) set forth in this application regardless of order, and is understood to include a process wherein said three steps are carried out simultaneously.

Therefore the invention set forth in claim 3 cannot be distinguished from the inventions set forth in documents 1 and 2.

For the same reasons, the invention set forth in claims 4 to 8 cannot be distinguished from the invention set forth in documents 1 and 2.

Claim 10

The invention set forth in claim 10 lacks novelty in the light of the inventions set forth in documents 1 and 2 cited in the international search report. Documents 1 and 2 set forth processes for producing bispecific antibodies, wherein by introducing knobs-into-hole it is possible to increase the ratio of antibodies containing a

first pair and a second pair, and that it is possible to increase the deactivation of the antibody composition.

Therefore the invention set forth in claim 10 cannot be distinguished from the inventions set forth in documents 1 and 2.

Claims 14 to 16

The invention set forth in claims 14 to 16 lacks novelty in the light of the inventions set forth in documents 1 to 3 cited in the international search report.

There is no discernible difference between the antibody and antibody composition set forth in claims 14 to 16 of this application and the bispecific antibody and composition containing said antibody set forth in documents 1 to 3.

Claims 17 and 19

The invention set forth in claims 17 and 19 lacks novelty in the light of the invention set forth in document 5 cited in the international search report.

Document 5 sets forth a vector wherein the expression of Fab fragments are induced by tetracycline, and *Escherichia coli* containing said vector.

It is therefore impossible to distinguish between the invention set forth in claims 17 and 19 of this application and the invention set forth in document 5.

Claim 20

The invention set forth in claim 20 lacks novelty in the light of documents 1 to 5 cited in the international search report.

There is no discernible difference between the cell set forth in claim 20 of this application and the cells set forth in documents 1 to 5.

Inventive Step

Claims 1 to 13

The invention set forth in claims 1 to 13 does not involve an inventive step in the light of documents 1 to 4 cited in the international search report.

Documents 1 and 2 set forth a process for producing a bispecific antibody having an Fc region, wherein "the H chain and L chain which constitute a first set disclosed in this application having a particular antigen recognition site" and "the H chain and L chain which constitute a second pair disclosed in this application having another antigen recognition site" are expressed simultaneously, and the formation of the first pair and the second pair and the bonding of said first pair and second pair via knobs-into-hole are carried out simultaneously. Documents 1 and 2 also indicate that antibodies are produced having antigen recognition sites comprising undesirable sets comprising the H chain which makes up the first pair and the L chain which makes up the second pair. In addition, documents 1, 3 and 4 indicate that "the V region of H chain and L chain which constitute a particular antigen recognition site" and "the V region of H chain and L chain which make up another antigen recognition site" are separately expressed in *Escherichia coli*, and that the respective H chain and L chain are bonded in advance, and their respective antigen recognition sites formed, after which the two antigen recognition sites are chemically bonded,

thereby efficiently producing the target bispecific antibody.

That being the case, in the process for producing a bispecific antibody having an Fc region set forth in documents 1 and 2, it would be easy for a person skilled in the art to refer to documents 1, 3 and 4 to separately express "an H chain and L chain which constitute a first pair disclosed in this application having a particular antigen recognition site" and "a H chain and L chain which constitute a second pair disclosed in this application having another antigen recognition site", and to bond their respective H chain and L chains in advance, forming a first pair and a second pair having an antigen recognition site, and subsequently bonding the first pair and second pair via knobs-into-hole, in order to prevent the production of antibodies having antigen recognition sites comprising undesirable sets and to efficiently produce the target bispecific antibody.

When doing so, a person skilled in the art would be capable of introducing an optimum expression regulating factor and carry out the expression of the aforementioned "H chain and L chain which constitute the first pair" and "H chain and L chain which constitute the second pair" in separate cells at different timing, to constitute the production process disclosed in this application.

Moreover, employing the configuration of the invention set forth in claims 1 to 13 of this application is not acknowledged to offer a special effect.

Claims 14 to 20

In addition, a person skilled in the art would be capable of using said production process to produce a bispecific antibody and a composition containing said

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

antibody, to produce a cell having the aforementioned vector introduced, and to produce a kit containing said vector.

Moreover, employing the configuration of the invention set forth in claims 14 to 20 of this application is not acknowledged to offer a special effect.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

(continued from Box IV.3)

first heavy chain and the first light chain is induced by a first expression regulatory factor and a vector wherein the expression of the second heavy chain and the second light chain is induced by a second expression regulatory factor.

The matter common to independent claims 10 and 15 (invention group D) relates to an antibody composition having an antibody containing the first pair and the second pair at a high ratio. The independent claim 17 (invention E) relates to a vector wherein the expression of a light chain or a heavy chain of an antibody is induced by an expression inducer.

Although invention groups A to E are common to each other in relating to an antibody comprising a heavy chain and a light chain, it is obvious that this matter has been publicly known. Thus this common matter cannot be considered as a special technical feature within the meaning of PCT Rule 13.2, second sentence.

Moreover, there is no common matter which appears to be a special technical feature within the meaning of PCT Rule 13.2, second sentence in arbitrary combinations of invention groups A to E.

Such being the case, invention groups A to E do not comply with the requirement of unity of invention.